FORMULATION, EVALUATION AND OPTIMIZATION OF METFORMIN HYDROCHLORIDE TABLET IP 500MG

A Dissertation submitted to

THE TAMIL NADU Dr.M.G.R. MEDICAL UNIVERSITY

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In partial fulfillment of the requirements for the award of the Degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

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OCTOBER 2016

DECLARATION

I hereby declare with immense pleasure and satisfaction that this dissertation work entitled "**Formulation, Evaluation and Optimization of Metformin Hydrochloride tablet IP 500mg"** was carried out by me under the guidance of **Dr.Manavalan R**, Professor and Head, Department of Pharmaceutics, R.V.S College of Pharmaceutical Sciences, Sulur, Coimbatore and **Mr. Santhosh (Industrial guide)** Production Manager, Kerala State Drug and Pharmaceutical Limited, Kalavoor, Alappuzha.

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TO WHOMSOEVER IT MAY CONCERN

This is to certify that Mr. Jinish C. George, S/o. C.A. George, M.Pharm Student of R.V.S College of Pharmacy, Dr. M.G.R. Medical University, Sulur, Coimbatore, Tamilnadu has undergone a Project Work in the title of **"FORMULATION, EVALUATION AND OPTIMIZATION OF METFORMIN HYDROCHLORIDE TABLET IP 500 MG"** in production and Quality Control Department of Kerala State Drugs and Pharmaceuticals Ltd at Kalavoor, Alappuzha during the period from 22.02.2016 to 21.04.2016.

He has put in his sincere efforts in completing the project work.

His Character and Conduct is good during the period.

KERALA STATE DRUGS & PHARMACEUTICALS LTD
KALAVOOR
ALAPPUZHA

28/07/2016

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CERTIFICATE

This is to certify that the research project work entitled **"Formulation, Evaluation and Optimization of Metformin Hydrochloride tablet IP 500mg"** is a bonafide genuine work carried out by **Mr. Jinish C George (Reg.No. 261410761**) in partial fulfillment of the requirements for the award of degree in **Master of Pharmacy in Pharmaceutics** of **The Tamilnadu Dr.M.G.R Medical University, Chennai** at RVS college of Pharmaceutical Sciences and in the production Department of **Kerala State Drug And Pharmaceuticals Limited**, Alappuzha, under the guidance and supervision of **Dr.Manavalan R,** Professor and Head (institutional guide) Department of Pharmaceutics R.V.S College of Pharmaceutical Sciences and **Mr.Santhosh** (industrial guide) Production Manager, Kerala State Drug and Pharmaceuticals Limited, Alappuzha.

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Jinish C George

Evaluation Certificate

Dissertation work : **Formulation , Evaluation and Optimization of Metformin Hydrochloride tablet IP 500MG .**

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INTERNAL EXAMINER **EXTERNAL EXAMINER**

Date:

Place:

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LIST OF ABBREVATIONS

S.NO	Abbreviation used	Meaning
1	ICH	International conference on harmonization
2	API	Active pharmaceutical ingredient
3	HPLC	High performance liquid chromatography
4	FT-IR	Fourier transform infrared spectroscopy
5	pH	Hydrogen ion concentration
6	BCS	Biological classification
7	LOD	Loss on drying
8	NLT	Not less than
9	NMT	Not more than
12	BD	Bulk density
13	TD	Tapped density
14	CI	Compressibility index
15	HR	Hausner's ratio
16	RH	Relative humidity
17	RPM	Rotations per minute
18	µg	Micrograms
19	g	Gram
20	mg	Milligram
21	kg	kilogram
22	mm	millimeter
23	mmHg	Millimeter mercury
24	nm	nanometer
22	^{0}C	Degree centigrade
23	Std	Standard
24	MCG	Mixer com granulator
25	cm^2	Centimeter square
26	SFP	Starch Fluid Paste
27	QS	Quantity sufficient

Abstract:

The basic aim is formulate, evaluate and optimize the Metformin Hydrochloride immediate release tablet by wet granulation technique. The Metformin is used as an ant diabetic drug. In order to obtain the best, nine different formulations were developed. Different binders, disintegrants and lubricants taken as variables. Pre compression parameters like Bulk density, True density, Angle of repose indicate all the formulations are showing good flow properties. The granules are compressed and tablets are evaluated for post compression parameters weight variation, Hardness, Friability, Disintegration and Dissolution parameters. Among all the formulations F9 is showing the release profile similar to the innovator. The compressed tablets was packed in blisters and subjected to stability studies at 40^0C and 75% RH, 25^0C and 60%RH. Samples were analyzed at regular intervals as mentioned in stability protocol. It may be concluded that Metformin tablet prepared as immediate release formulation compared to conventional formulations.

1. INTRODUCTION

Oral drug delivery is the fastest and more preferred route for the drug administration is also the largest and oldest segment of the total drug delivery market. Various types of drug delivery systems are available to get better therapeutic action of drug, out of which immediate release drug delivery system is gaining more importance because of their wide advantages over others like ease of administration , convenience and noninvasiveness.[1]

Metformin was discovered in 1922.Study in humans began in 1950s by French physician Jean Sterne. It was introduced in France in 1957 and the United States in 1995.It is on the World Health Organization's List of Essential Medicines, the most important medications needed in a basic health system. Metformin is believed to be the most widely used medication for diabetes which is taken by mouth [2] .Metformin hydrochloride (MH) is an oral hypoglycemic drug that has been used for the management of the non-insulin-dependent diabetes mellitus. It is taken in tablets of 500 and 850mg, with low and the incomplete absorption by the gastrointestinal tract, the usual dose being 2g/day and the maximum dose 3g/day.

1.1 IMMEDIATE RELEASE DRUG DELIVERY SYSTEM [3,5,6]

Immediate release tablet dosage forms are those which dissolved and get rapidly disintegrate to release the medicaments to produce rapid action. It should dissolve or disintegrate in the stomach within a short period of time. It should exhibit low sensitivity to environmental conditions as humidity and the temperature. Be manufactured using conventional processing and packaging equipment at low cost. It should not leave minimal or no residue in the mouth after oral administration. It produces rapid dissolution and absorption of drug, which may produce rapid onset of action. Immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluents or carriers are does not prolong ,to an appreciable extend, the rate of drug release and/or

absorption .This term excludes formulations which are adapted to provide for "modified", "controlled", "sustained", "prolonged", "extended", or "delayed" release of drugs.

For immediate release tablet disintegrates play a major role in ensuring that tablet matrix break up on the contact with the fluid present in the stomach to allow the release of active component which then become available in whole or in part, for absorption from gastrointestinal tract.

Criteria for immediate release drug delivery system [4]:

Immediate release dosage form should –

- In the case of the solid dosage forms it should be dissolve and disintegrate in the stomach within the short period of the time.
- In the case of the liquid dosage forms it should compatible with taste masking.
- It should not leave minimal or no residue in the mouth after the oral administration.
- It should have pleasing mouth feel.
- It should be portable without fragility concern.
- It act rapid dissolution and absorption of drug, which may produce the rapid onset of action.
- Be manufactured by using the conventional processing and packaging equipment at low cost.
- It exhibit low sensitivity to environmental conditions like humidity and temperature.

The merits of immediate release drug delivery system [4, 15]:

- It allows the high drug loading.
- Improved compliance.
- Improved bioavailability, solubility.
- It ability to provide advantage of liquid medication in the form of the solid dispersion.

- Immediate release drug delivery system will produce decreased disintegration and the dissolution times.
- It improved the solubility of pharmaceutical preparations.
- Immediate release drug delivery system allow the high drug loading
- It effective on cost.
- Amenable and adaptable to existing processing and the packaging machinery.
- The ability to provide advantage of liquid medication in the form of solid preparations.

1.2 ANTIDIABETICS [2,16,13,14]

Drugs used in diabetes treat diabetes mellitus by lowering glucose levels in the blood. With the exceptions of insulin, exenatide, liraglutide and pramlintide, all the administered orally and are thus also called oral hypoglycemic agents or oral anti hyperglycemic agents. There are different classes of anti diabetic drugs, and there are different classes of anti-diabetic drugs, and their selection depends on the nature of the diabetes, age and situations of the person, as well as other factors. The Diabetes Mellitus describes a metabolic disorder of multiple aetiology. The effect of Diabetes Mellitus includes dysfunction, failure and long term damage of various organs. In most severe form of DM nonketotic hyperosmolar state may develop.

Diabetes mellitus type1

It is a disease caused by the lack of insulin .it comes about due to the loss of pancreatic function. The loss of pancreatic function may be due to disease or injury to the pancreas which ultimately leads to loss of optimum glycaemic control. Thus, insulin needs to be injected subcutaneously twice daily to compensate for the needs of the body (also referred as insulin-dependent-diabetes mellitus, and juvenile diabetes)

Diabetes mellitus type 2

There is a decrease in the body's secretion and sensitivity to insulin, which usually caused by obesity. It is a disease of insulin resistance by cells. Type 2 diabetes mellitus is the most common type of diabetes. Treatments include

1) Agents that increase the amount of insulin secreted by the pancreas.
2) Agents that increase the sensitivity of target organs to insulin.
3) Agents that decrease the rate at which glucose is absorbed from the gastrointestinal tract.

Several groups of drugs , mostly given by mouth , are effective In type 2 ,often in combination .The therapeutic combination in type 2 may include insulin, not necessarily because oral agent have failed completely, but in search of a desired combination of effect. The great advantage of injected insulin in type 2 is that a well-educated patient can adjust the doses. When blood glucose levels measured by the patient, usually with a simple meter, as needed by the measured amount of sugar in the blood.

Non insulin-dependent diabetes mellitus, maturity onset diabetes mellitus: There is no loss or moderate reduction in β cell mass; insulin in circulation is low ,normal or even high, no anti β cell antibody is demonstrable; has a high degree of genetic predisposition; generally has a late onset(past middle age).Over 90% cases are type2DM.Causes may be:

- Abnormality in gluco-receptor of β cells so that they respond at higher glucose concentration or relative β cell deficiency.
- Reduced sensitivity of peripheral tissue to insulin: reduction in number of insulin receptors 'down regulation' of insulin receptors.
- Excess of hyperglycemic hormone, causes relative insulin deficiency the β cells lag behind.

1.3 ORAL HYPOGLYCAEMIC DRUGS [17,18]

More than 95% of Type2 Diabetic patients in our country, and it have already reached in epidemic proportions, mainly in Urab India. Possibly India shall have about 57.2 million diabetics by the year of 2015. These drugs lower blood glucose levels and are effective orally. The chief drawback of insulin is –it must be given by injection. Orally active drugs have always been searched.

- **SULFONYLUREAS**
  - First generation
    - Tolbutamide
    - Chlorpropamide
  - Second generation
    - Glibenclamide
    - Glipizide
    - Gliclazide
    - Glimepride

- **BIGUANIDES**
  - Metformine

PHENYL ALANINE ANALOGUES

- Repaglinide
- Nateglinide

- **THIAZOLIDNEDIONES**
  - Rosiglitazone
  - Pioglitazone
- **α GLUCOIDASE INHIBITORS**
  - Acrbose
  - Miglitol

1.5 TABLETS [7,8,9,15,16]

Tablets are solid dosage forms, flat or biconvex in shape, prepared may be swallowed or being chewed. Some types of tablets are in dissolved or dispersed in water. And also implants and passerines also be presented in form of tablets. Tablets may vary in size, shape, and weight depending on the medical substances and mode of administration. The manufacture of oral dosage form is a complex multistage process. The starting material changes their physical characteristics. Traditionally dry granulation and wet granulation are used.

Advantages of the tablets

- Accuracy of dose can be maintained since tablet is a solid dosage form.
- Ease of handling and the easy of packing over the other dosage forms.
- Identification of the product is easy and marking done with the help of grooved punches and printing with the edible ink.
- Compare to parental dosage forms, not required for other persons like doctors or nurse -that is self administration is possible.
- In comparison with capsules, tablets are the more water proof.
- Different types of the solid dosage forms are available like floating, buccal, colon targeting, effervescent, chewable, soluble etc.
- Emergency supplies can be carried by patients,
- Easy to transport in bulk.
- Longer expiry period and the minimum microbial spillage owing to lower moisture content.
- Organoleptic properties can be improved by the coating method.
- The solid dosage forms are not a sterile dosage forms, stringent environmental conditions are not required in the tablet department.

Disadvantages of tablet

- It produce slow onset of action as compared to liquid orals, capsules and parental.
- Cannot swallow tablet who patients undergoing radiotherapy.
- Difficult to convert high dose poorly compressible API in to tablet of suitable size for human use
- Tablet dosage forms are difficult to formulate with poor wet ability, slow dissolution in to a tablet.

1.5.1 TYPES OF TABLETS [8,9,10]

Different types of tablets are developed. With advancement in technology, modification in tablets to achieve better bioavailability , newer and efficient dosage forms are being developed,

Tablets here are classified by their route of administration.

A. Oral tablets for ingestion.

This class of formulation is the most popular worldwide and the major attention of the researcher is towards this direction. These tablet dosage forms are swallowed along with sufficient quantity of water exception is chewable tablet. Now 90% of the solid dosage forms are ingested orally.

B. Multiple compressed tablets

- Layered tablet
- Floating tablet
- Chewable tablet
- Compression coated tablet
- Delayed action tablet
- Colon targeting tablet
- Dispersible tablet

C. Tablets used in oral cavity

Tablet under this category avoid the first pass metabolism, decomposition in gastric environment, nausea tic sensation and gives rapid onset of action. These groups are aimed to release API in oral cavity or to provide local action on this region.

- Mouth dissolved tablet
- Lozenges and troches
- Buccal tablet dental cones

D. Tablets administered by other routes

These are administered by other route except oral cavity and so drugs are avoided from passing through gastro intestinal tract. These types of the tablets may be directly placed below the skin or inserted in other body cavities to be absorbed to systemic circulation from the site of application.

- Vaginal tablet
- Implants

E. Tablets used to prepare solution

These groups of tablets are required to dissolve in water or other solvents before administration. This solution may be for parentral applications or ingestion or topical use depends upon type of medicament used.

- Effervescent tablet
- Hypodermic tablet

1.6 ROLE OF EXCIPIENTS IN SOLID DOSAGE FORM [11,12,4]

The excipients are balance the properties of the immediate release dosage forms. The excipients are very important in understanding the chemistry of the interactions with the actives. Excipients are general and can use for a broad range of activities.

A. Diluents or fillers

Diluents or fillers are added where the quantity of active ingredient is small or difficult to compress.

Eg; lactose, mannitol

B. Binders

These are the adhesives that are added to the tablet formulation. The role of binders is to provide the cohesiveness essential for the bonding of the solid particles under compaction to form a tablet in a wet granulation process, binderes promote size enlargement to provide granules, and they improve flow ability.

Eg; starch, gelatin, tragacanth

C. Disintegrants

The major role of this is helping the tablet break up after the administration of tablet. The super disintegrants is an excipient which is added to a tablet or capsule to break up the compactable mass .it effective in the lower concentration and less effective on compressibility and flow ability.

Eg; sodium starch glycolate, cross carmellose

D. Lubricants

It prevents powders from sticking to the metal component of the tablet press and the tablet press toolings. It also helpful for removal of grittiness and also assist the drug transport mechanism from mouth to down the stomach.

Eg; talc, aerosol

E. Glidants

Glidants are the agents that act as a reducing inter particular friction

Eg; magnesium state

F. Adsorbents

These are the substances included in the formulations that are capable of holding fluid in an apparently dry state. Fluid extracts or oil soluble drugs can be mixed with adsorbents then granulated and compressed in to tablets.

Eg; fumed silica, microcrystalline cellulose, magnesium carbonate

G. Colorants

Colorants are added for the product identification.

1.7TABLET MANUFACTURING PROCESS [8,9,10,30]

In the tablet manufacturing process the granulation is the important process. The particles given in granulation process will improve the content uniformity, flow and compression characteristics, reduce segregation and eliminate excessive amount of particles. The results improve the yield, reduced the tablet defects. The objective of the process is to produce a quality tablet.

Table no: 1 Steps involved in the tablet manufacturing process.

S.NO	PROCESSING STEPS	DIRECT COMPRESSION	WET GRANULATION	DRY GRANULATION
1	RAW MATERIALS	YES	YES	YES
2	WEIGHING	YES	YES	YES
3	SCREENING	YES	YES	YES
4	MIXING	YES	YES	YES
5	COMPRESS	YES	NO	YES
6	WET MASS	NO	YES	NO
7	MILLING	NO	NO	YES
8	DRYING	NO	YES	NO
9	SHIFTING	NO	YES	YES
10	MIXING	NO	YES	YES
11	COMPRESSION	NO	YES	YES

1.8 STABILITY STUDY AS PER ICH GUIDELINES [35,36]

Stability is defined as the capacity of the drug product to remain the established specification to maintain its strength, identity, purity, throughout the expiration dating period.

The objective of the stability study determine the shelf life, the shelf life means the time period of storage at a specific condition within which the drug product still meets its established specification. Stability is the essential part for the quality, safety and efficacy of product. This is not of sufficient stability results in changes in physical as well as chemical characteristics.

The chemical stability of drug is of great importance since it becomes less effective as it undergoes degradation. Microbiological instability of a sterile drug product could also be hazardous. Stability valuation of drug substance is the key to drug quality as it determines the efficacy of dosage form. In fact stability testing issues are responsible for number of audit findings by the regulatory agencies. Stability testing provides evidence that the quality of drug substance change with time under the influence of various environmental conditions such as the humidity, temperature etc. Stability studies consist of the series of test in order to maintain a assurance of stability of drug product, involved drug product packed in specified packaging material and stored in definite storage conditions within the determined time period.

➢ AIM OF STUDY

Development and evaluation of Metformine hydrochloride IP 500mg tablets by using nine optimized formulations.

➢ OBJECTIVE OF STUDY

- Carrying out literature survey of the drug molecules
- Formulation of the tablets using different trails
- Analyzing the trial samples
- Optimizing the final formula

3. PLAN OF WORK

- Development of final formula
    - Literature collection for trial product
    - Pre formulation studies
    - Formulation of trail products
    - Dissolution studies of formulations
    - Finalization of quantitative formula

- ***Adimoolam Senthil, Prasanthi sri et al(2013)[41]*** **-** Metformin HCl is an oral anti-hyperglycemic drug used for the treatment of non-insulin dependent diabetes mellitus. Metformin hydrochloride is a highly water soluble, hygroscopic and odorless. Consequently, there is a need to provide a free-flowing and cohesive Metformin hydrochloride capable of being directly compressed into the tablets with an acceptable *in vitro* dissolution profile. Different types of directly compressible excipients (disintegrant, diluents, binder) were evaluated to find the maximum amount of Metformin HCl to be loaded in tablet for direct compression. An approach to further increase Metformin hydrochloride was designed by employing recrystallization technique such as anti-solvent method. Metformin hydrochloride was recrystallized in the presence of different concentration of PVP K30 for different intervals of recrystallization time. A 3^2 full factorial design was employed to get optimum processing conditions. The recrystallized Metformin hydrochloride was explored for preparation of the sustained release tablet by using the hydroxypropylmethyl cellulose K15 M.Weibull model is adopted for release profile.

- ***Dr K.L.Senthilkumar,R.P Ehizilmuthu et al(2011)[42]*** **-** The Study aim to development and evaluation of Metformin sustained release tablets using different polymers as release retarding agent. It is studied that formulation of sustained release tablet of Metformin containing 13 % HPMC K100 with binder PVP K30 i.e. optimized formulation of sustained release tablets for 10 hour release as it fulfills all the requirements for sustained release tablet. The sustained release tablets of Metformin hydrochloride prepared by wet granulation and direct compression method. The granules for the matrix tablet were prepared according to the angle of repose, total drug content and bulk density. The different in amount of polymer was largely dependent the viscosity grade, gel swelling and diffusion behavior of HPMC.

- ***Rikin Patel, Nidhi Shah et al(2011)[43]-*** Quality cannot be assured by in-process and finished product testing. This study about the process validation of Metformine hydrochloride and Glimipride extended release bilayered tablet. The quality should be built into the various stages of process of manufacturing steps. To obtain the quality specifications in finished product, various manufacturing processes with various manufacturing steps including critical process parameters should be controlled. The

critical process parameters can be evaluated by performing various tests at different stages. In this study taken three process validation batches of same size, method, equipment and validation criteria were taken. The critical parameters involved in the process are sifting, granulation, pre compression and compressions were evaluated. Different steps of manufacturing procedures were evaluated for in the process of pre compression and post compression steps; acceptable moisture content after drying, acceptable particle size distribution, blend uniformity, bulk density, weight variation, thickness, hardness, %friability, dissolution, disintegration after compression. The results of these parameters indicated that this process validation data provides high degree of assurance that manufacturing process produces product meeting its predetermined specifications and quality attributes. So, manufacturing process of Metformin Hydrochloride and Glimepiride belayed tablet was considered as validated tablet. The three batches produce acceptable uniform results.

- ***Manoj charde,S Jayani et al(2011)[44]-*** The purpose of formulation and evaluation of immediate release tablet of Metformin Hydrochloride on the basis of laboratory scale method. It prepared by the process of wet granulation method. To obtain the best optimized product from ten different formulations. The different types of excipients like disinitegrants, binders and lubricants are taken as variables. Mainly in this formulation contains PVPK-30 and also use PVPK-90.The physical properties and in vitro release profile showing the best comparable with reference product. The in vivo drug release can be checked and also carry the toxicity study. By making the combination with the some of new drugs the novel formulation can developed.

- ***Villarroel stuart,Yclement et al(2015)[45]-***This study about the comparing the dissolution profile of 7 batches of Metformin Hydrochloride formulations in simulated intestinal fluid. The dissolution test used to evaluate the pharmaceutical product performance. It includes the two products with trade name Glucophage in simulated intestinal fluid at ph 6.8.The dissolution were carried by paddle type apparatus used. It worked at 75 rpm in 900ml of simulated intestinal fluid at 37 ± 0.5^0c.1.25ml sample were removed at definite intervals of time of which 100µl diluted with the fresh medium. It is then analyzed by spectrophotometrically at 233nm.The drug content between each of the formulations is 99% and 103%.And

formed six Metformin Hydrochloride formulations that fulfilled WHO requirements. The two innovator product with same trade name were similar biopharmaceutical quality but statistically different.

- ***Pelango, Ramesh et al(2014)[46]-***This study involved in comparative release analysis of commercial Metformin tablet .It involves the about five commercial brand were analyzed with their chemical content , drug release and physical characters .Randomly select the commercial brand of Metformin Hydrochloride selected and the groups were coded and analyzed. These tablets are analyzed by their shape, size, color, weight, friability, disinitegration, purity and drug content. All types of tests are done within product expiration dates. Purity determined by ultra violet spectro photometer .Based on the physical inspection Brand c500 is the smallest and Brand d500 is largest in size. All the brands had weight in loss less than 1% after the test of friability required content is present in brand AXL500 and brand d500.The sustained release drug dosage forms designed for maintain the therapeutic blood or tissue levels of drugs.
- ***Madhusudhan Reddy et al(2013) [47]-***Formulation and evaluation of sustained release matrix tablets of Metformin Hydrochloride is prepared using Metformin, Xanthum gum, Gar gum, MCC, Magnesium state, PVP, IPA. It prepared by using of different proportion of the Xantham gum and Guar gum. The mostly natural excipents are having better sustaindility than marketed Metformin Hydrochloride tablet that prepared with the synthetic polymers. In this case the dissolution study proves that matrix tablet is shown 87.02%of drug release in 8hr where as marketed drug shown 105.6% drug release in 8hr.
- ***Kamoran Alam,Fraya zafar et al(2013)[48]-*** This study involved in the development and evaluation of Metformin Hydrochloride 500mg sustained release tablets. Two hydrophilic and hydrophobic formulations were formulated by the independent variables using the Dextrose ranged from 0-30% and plasdone S360 ranged from 19-49%.The dissolution medium is used as a phosphate buffer pH6.8.Controlled release tablets are more preferred in the case of management of therapy due to its excellent compliance, decrease side effect and dose and the enhance safe use of high potency compounds. Results of this study indicated that all the formulations are under the first

order kinetics. The results of this study indicated that FHP1, batch1, and batch2 were found similar with reference formulation at pH 6.8.

- ***Margret Chandria et al (2007)[49]-*** This study involved in the formulation and evaluation of extended release tablet of Metformin Hydrchloride tablet. The extended release Metformin tablet prepared by the wet granulation technique by using the different concentrations of polymers like Hydroxy propyl methyl cellulose and carbopol71G. The formulated tablet undergoes the pre compression study and the post compression study. The lubricating agent is used as Magnesium stearate. The punch size is using length19.7mm and 7.3mm width. The dissolution test is carried by using apparatus type2 paddle type using 6.8 phosphate buffers. F10 is matched with the innovator because it contains both HPMC K100 and carbopol 71G.

- ***Ramteke K H et al(2012)[50]-*** The purpose of formulation of Metformin Hydrochloride in to beads, it gives the sustained release action of Metformin .This formulation is prepared by the ionotropic extended release technique. The calcium and aluminium is used as a cross linking agent. The beads prepared by the Das Mk. The alginate beads produce sustained release action about 10hr.

- ***S M Moazzem Hossen et al(2014)[51]-*** The prime objective of this study is development of immediate release Metformin Hydrochloride tablet by using sodium starch glycolate, Collidon CL and Crosscarmellose sodium as super disintegrants. These are add in different concentrations 2-5%. Aerosol-200 is used to provide good flow property, Magnesium stearate as a lubricant. The formulations are evaluated for pre compression and post compression parameters. This study contains the effect of superdisintegrant agents. It concluded that high concentration of superdisintefrants produce high percentage release while lower concentration caused low release.

- ***Narasimharan R et al(2011)[52]-*** This study involved the design and evaluation of Metformin Hydrochloride extended release tablets by direct compression method. Having an elimination half life of 5±2hrs and it maximum daily dose is 1000mg. The rate of drug release was in following order HPMC K15M>HPMC K100M>HPMC K200M. The drug release was faster in the formulation five due to HPMC K200.The wet granulation method was better choice to extend the drug release for 12hr.

5. DRUG AND EXCIPIENTS PROFILE.

5.1 METFORMINE DRUG PROFILE [23]

Figure no: 1 Structural formula

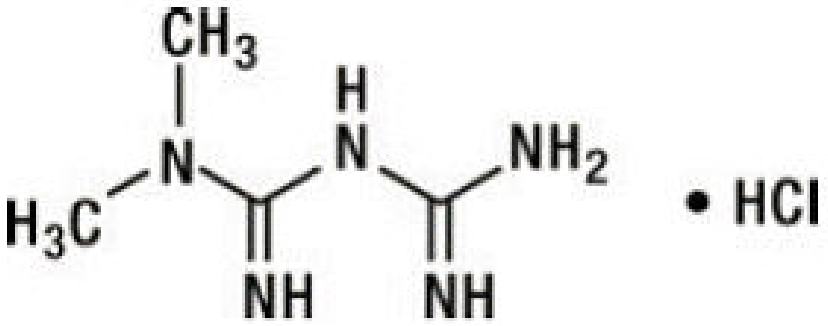


Table no:2 Metformin drug profile

PROPERTIES	INFORMATION
Molecular formula	$C_4H_{11}N_5.HCl$
Molecular weight	165.6
IUPAC name	N,N-Dimethylimidodicarbonimidic diamide
Macroscopic appearance	White crystalline powder
Half life	4-8.7hr
Solubility	Freely soluble as HCl salt
pH	6.68
pKa	12.4
Use	Oral hypoglycemic drug

Mechanism of action [19,20,21,22]

Hypoglycemic

Metformin decrease hyperglycemia primarily by suppressing glucose production by the liver .The average person with type 2 diabetes has three times the normal rate of gluconeogenesis; Metformin treatment reduces this by over one third. The molecular mechanism of Metformin is incompletely understood: inhibition of mitochondrial respiratory chain, activation of AMP activated protein kinase(AMPK),inhibition of glucagon-induced elevation of cAMP with reduced activation of protein kinase A, Inhibition of mitochondrial glycerophosphte dehydrogenase , and effect on gut microbiota have been proposed as potential mechanisms.

5.2 EXCIPIENTS PROFILE

GELATIN[24,25]

Table no: 3 Gelatin excipient profile

Empirical formula	$C_6H_{12}O_6$
Sources	Thermal denaturation of collagen , isolated from animal skin and bones, also extracted from fish skins
Description	Light amber to faintly yellow, Transulcent flakes sheets. Brittle when dry
Solubility	Readily dissolves in hot water ,it also soluble in most polar solvents,
Melting point	The upper M.P is below human body temperature
Viscosity	Viscosity of gelatin/water mixture is greatest when the gelatin concentration is high and the mixture is kept cool at about 4^0C
Loss on drying	Not more than 16.0%
Storage	Store protected from moisture
Application	Gelling agent, suspending agent ,used in pharmaceuticals, photography and cosmetic manufacturing

SODIUM STARCH GLYCOLATE[33]

Table no: 4 Sodium starch glycolate excipient profile

Non propriety names	Explotab , Vivastar
Synonyms	Sodium salt of carboxy methyl ester of starch
Empirical formula	C_2H_5ONa
Molecular weight	500000 - 11000000
Description	Weight to off white, Tasteless, Odorless, Relatively free flowing powder.
Solubility	Practically insoluble in organic solvents. It absorbs water rapidly.
Functional categories	Disintegrant, Dissolution aid, Suspending agent.
Melting point	338^0C
Stability and Storage	Store in well closed container to protect from humidity
Incompatibilities	Mostly compatible with all other tabulating ingredients.
Applications	Suspending and gelling agent

TALC[27]

Table no: **5** Talc excipient profile

Non proprietary names	B.P- Purified talc Ph Eur-Talcum USP-Talc
Synonyms	At talc, Hydrous magnesium calcium silicate, Hydrous magnesium silicate, Magsil osmanthus, Soapstone
Empirical formula	$Mg_3Si_4O_{10}(OH)_2$
Molecular weight	379.27
Description	Talc is very fine, white to grayish white, odorless, unctuous, crystalline powder. It adheres rapidly to the skin.
Melting point	150^0C
Solubility	Not soluble in water and slightly soluble in dilute mineral acids insoluble in water and ethanol.
Functional categories	Anti caking agent, Glidant, diluents and lubricants for tablets and capsules.
Stability and storage conditions	Talc is stable material and may be sterilized by heating at 160^0C for not less than 1hr. Talc should stored in well closed container in a cool and dry place.
Incompatibilities	Incompatible with quaternary ammonium compound.
Applications	Lubricant, Diluents, Dissolution retardant in controlled release formulations.

METHYL PARABEN[28]

Table no: 6 Methyl paraben excipient profile

Non proprietary names	Sodium methyl parahydroxy benzoate, Methyl paraben sodium salt.
Synonyms	Methyl 4-OH benzoate, Nipaginm
Empirical formula	$C_8H_8O_3$
Molecular weight	152.14732
Description	Soluble in water at 25^0C, slightly soluble in benzene, CCl4, ethanol. Ether, acetone, DMSO, methanol
Melting point	125 -128^0C
Functional category	Preservative
Incompatibilities	Incompatible with alkalis and metal salt
Stability and storage conditions	Stable at ambient temperature and under normal conditions of use dust may explosive. Keep container closed when not in use.
Solubility	Soluble in water at 25^0C, slightly soluble in benzene, CCl4, ether.
Applications in pharmaceutical industry	It is an antifungal agent, often used in variety of cosmetics and personal care products. It is used as food preservatives.

PROPYL PARABEN[29,37]

Table no: 7 Propyl paraben excipient profile

Non proprietary names	Propyis parahydroxy benzoate(Latin) Propyl 4-hydroxybenzoate(German) Propyl (Parahydroxy benzoate(French)
Synonyms	Propyl butex, Propyl chemosept, Propyl 4-hydroxybenzoate,Parahydroxy benzoic acid propyl ester
Empirical formula	$C_{10}H_{12}O_3$
Molecular weight	180.2
Description	White crystalline powder,colourless crystals or white powder or chunky white solid odourless or faint aromatic odour,low toxicity and tastes.
Solubility	Water soluble
Melting point	95-98^{0}C
Stability and storage conditions	Stable, stability maximum occurs at pH 4-5
Functional categories	Preservative, Food additive
Incompatibility	Incompatible with alkalies and metal salts
Application in pharmaceutical industry	An antimicrobial preservative in packaged foods, pharmaceuticals, cosmetics.

STARCH[26]

Table no: 8 Starch excipient profile

Non proprietary names	Amylum, Polysacharide
Synonyms	Starch 1500,Starch LM
Empirical formula	$(C_6H_{10}O_5)_n$
Molecular weight	Depends on extend of gelatinization
Description	odorless, tasteless
Functional categories	Thickening agent ,stiffening agent, gluing agent
Solubility	Insoluble in cold water or alcohol, become soluble on heating
Stability and storage conditions	Starch is stable and should be stored in a well closed container in a cool and dry place.
Incompatibilities	Incompatible with strong acids, alkali. Avoid mixing with strong oxidizing agent
Applications	Binder, Diluent, lubricant

6. METHODOLOGY

6.1 PREFORMULATION STUDY[31]

Preformulation study is the investigation of physical and chemical properties of a drug substance alone and when combined with excipents. It is the first step in the rational development of dosage forms. The first learning phase is pre formulation. It involves reaching the goal of designing optimum drug delivery system by application of biopharmaceutical principles to physiochemical parameters.

A) Physical chemical evaluation of drug molecules

- Description
- Solubility
- pH
- Melting point
- Chemical nature
- Hygroscopicity
- Loss on drying
- Particle size determination
- Flow property

B) Compatibility study of drug and excipients

The information obtained from the preformulation studies indicates many of the subsequent events and approaches to be taken in to consideration during formulation development.

A) PHYSICO CHEMICAL PARAMETERS [32,33,34]

1) Description

A detailed account of the certain or salient aspects, characteristics, or features of a subject matter or something seen, here or otherwise experienced or none.

2) Solubility

Solubility is a chemical property referring to the ability for a given substance, the solute, to dissolve in a solvent. It is measured in terms of the maximum amount of solute dissolved in a solvent at equilibrium.

3) pH

It is the negative of the logarithm to base 10 of the concentration, measured in units of moles per liter of hydrogen ions. More precisely it is the negative of the logarithm to base 10 of the activity of the hydrogen ion.

4) Melting point

A melting point is the temperature at which a solid substance assumes the liquid conditions. At the melting point solid and the liquid phase exist in equilibrium. The melting point of substance depends on pressure and is usually specified standard pressure.

5) Chemical nature

Solubility, stability, bioavailability etc. of a substance depends on its chemical nature and this information helps to design a suitable dosage form.

6) Hygroscopicity

Hygroscopicity is the measurement of a materials ability to absorb or release water as a function of humidity (i.e., water activity) The ideal way of hygroscopicity would be create a moisture sorption isotherm by looking at the changing water content vs. relative humidity and temperature.

Table no: 9 Classification based on hygroscopic nature

S.NO	NATURE OF SAMPLE	RESULT OF THE DETERMINATION
1	Deliquescent	Sufficient water absorbed to form a liquid
2	Very hygroscopic	Increases in mass equal to or more than 15%
3	Hygroscopic	Increases in mass less than 15% and equal to or more than 2%
4	Slightly hygroscopicity	Increases in mass less than 2% and equal to or more than 0.2%

7) Loss on drying

This is widely used test method to determine the moisture content of the sample, although occasionally it may refer to the loss of any volatile matter from the sample. Therefore this method does not usually refer to the molecularly bound water or water of crystallization.

8) Particle size determination

Particle size analysis is the collective name of the technical procedures or laboratory techniques, which determine the size range and or the average or mean size of the particles in a powder or liquid sample. It is an important method for research

in industrial development. The particle size of Metformin hydrochloride was done by sieving method.

Sieve analysis

Table no: 10 Classification based on %of sample retained or passed on test sieves.

S.NO	NATURE OF SAMPLE	RESULT OF DETERMINATION
1	Coarse powder	NLT 95% of the sample mass pass through 14# and NMT 40% pass through 36#
2	Moderately coarse powder	NLT 95% of the sample mass pass through 25# and NMT 40% pass through 60#
3	Moderately fine powder	NLT 95% of the sample mass pass through 36# and NMT 40% pass through 100%
4	Fine powder	NLT 95% of the sample mass pass through 100# and NMT 40% pass through 150#
5	Very fine powder	NLT 95% of the sample mass through 150# and NMT 40% pass through 200#
6	Super fine powder	NLT 90% by number of particles are less than 10µm

9) Flow property measurement:

It is a very important parameter to be measured, It affects the mass of uniformity of the dose .It is usually predicted in terms of angle of repose, bulk density, tapped density.

Angle of Repose

The angle of repose of granular materials is the steepest angle of descent or dip relative to the horizontal plane o which a material can pile without slumbing. At this angle the material on the slope phase is on the verge of sliding

$$\Theta = \tan^{-1} h/r$$

Where,

Θ = Angle of repose

h = Height

r = Radius

A funnel fixed at a height approximately of 2-4 cm over the plat form. The loose powder slowly passed along the wall of funnel, till the cone of the powder formed. Determine the angle of repose by measuring the height of the cone of the powder and the radius of the heap of the powder.

Table no: 11 Flow properties and the corresponding angle of repose

S.NO	FLOW PROPERTY	ANGLE OF REPOSE(DEGREE)
1	Excellent	25-30
2	Good	31-35
3	Fair	36-40
4	Passable	41-45
5	Poor	46-55
6	Very poor	56-65
7	Very Very poor	>66

Bulk Density (BD) and Tapped Density (TD)

Bulk density of a compound varies substantially with the method of crystallization, milling or formulation. When one considers the size of a high –dose

capsule product or the homogeneity of low dose formulations in which there are large difference in drug and the excipient densities. In addition to bulk density, it is frequently desirable to know the true density of a powder for computation of void volume or porosity of packed powder beds.

An accurately weighed quantity of the granules /powder was carefully poured into the graduated cylinder and volume was measured. Then the graduated cylinder was closed with lid and set into the tap density tester (USP). The density apparatus was set for 100 tap after that the volume was measured and continued operation till the two consecutive readings were equal. The bulk density and the tapped density were calculated using the following formulae.

Bulk density = Weight of sample in gram / Volume occupied by the sample

Tapped density = Weight of sample in gram / Tapped volume

Compressibility index (CI) and Hausner ratio (HR)

The compressibility index and Hausner ratio methods are used for predicting powder flow characteristics. Both the compressibility index and the Hausner ratio were determined by using bulk density and the tapped density of a powder.

C.I = Tapped – Untapped*100/ Tapped.

H.R = Tapped density / Bulk density.

Table No: 12 Relation of flow property with Hausners ratio & compressibility index

Compressibility index (%)	Flow character	Hausners ratio
≤10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very Very poor	>1.60

10)Moisture content : By Karl fisher method

Transfer the 35-40ml of methanol to the titration vessel and titrate with the reagent to the electrometric or visual end point to consume any moisture that may present. Weigh accurately 0.2-0.5gm of powdered sample, and quickly add to the titration vessel and perform the test potentiometrically.

6.2 MATERIALS AND EQUIPMENTS

Table No: 13 List of materials for preparation of Metformin

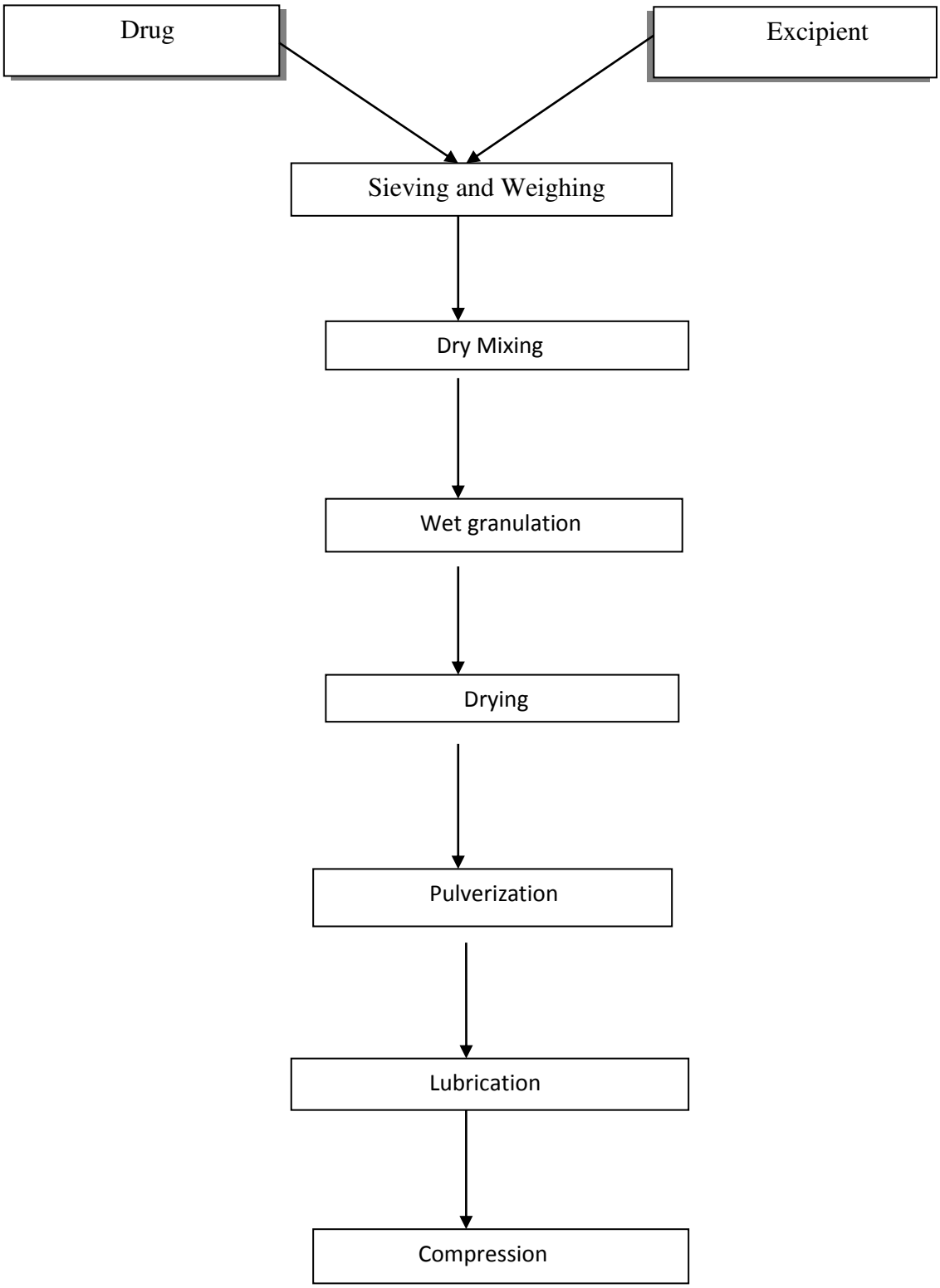
S.NO	Name of materials used	Specifications	Use
1	Metformin	IP	Active ingredient
2	Starch	IP	Diluent
3	SFP	IP	Thickening agent
4	Gelatin	IP	Thickening agent
5	Methyl paraben	IP	Preservative
6	Propyl paraben	IP	Preservative
7	Talc	IP	Lubricant
8	Sodium starch glycolate	USP	Super disintegrant

Table no: 14 List of equipments used for formulation of tablet

S.NO	EQUIPMENTS USED	MANUFACTURER
1	Electronic weighing balance	Mettler , Switzerland
2	Electronic weighing balance 1kg	Averi India
3	Max mixer	Innofab India pvt.ltd, Hyderbad
4	Fluidized bed dryer	Alliance ,Bombay
5	Cad mill	Cadmach, Ahemmadabad
6	Blender	Bhuvaneswari, Madras
7	Tablet Compresssion mechine 45 station double rotary	Cadmach, Ahamedabad
8	Electronic LOD measurement apparatus	Sartorius, Germany
9	Friability tester	Veego ,Mumbai
10	Tablet hardness tester	Electrolb, Mumbai
11	Bulk density apparatus	Electrolab, Mumbai
12	Dissolution apparatus USPII	Veego, Mumbai
13	Tablet Disintegration test apparatus	Veego, Mumbai
14	FT-IR Spectrophotometer	Perkin Elmer,USA

6.3 PROCESS INVOVED IN TABLET PRODUCTION

Figure No:2 Flow chart process involved in tablet production.



Steps involved in Formulation of Metformin granules

Preparation of Raw materials:-

The raw materials and active pharmaceutical ingredients are weighed and sieving through the 22#mesh and check the weight of the raw materials. And they are collected in suitable baskets.

Dry mixing:-

Check weight of the materials and sift pregelatinized starch through 40#mesh load in to mixer come granulation. Dry mix for 15min at low speed.

Wet granulation:

Add binder solution to above powder which mixing for 5-15 min in mixer at slow speed. Change mixer speed to fast and mix for 5-15 min till required end point achieved. If required add additional wet mass through mixer come granulator hole. Switch granulator at fast speed and mix for next 15 minute. And then pass through the cad mill to get required type of granules. And unload in to Fluidized bed dryer bowl, scrap material from cad mill bowl to Fluidized bed dryer bowl at end of batch.

Drying:

Dry the wet milled granules in Fluidized bed dryer for 30minute and check for loss on drying for 30minute and rake again. Dry till loss on drying at not more than o.5%.Check loss on drying at 90^0C.

Pulverization:

Pass the dried granules in to the cad mill. And add additional quantity of ingredients then, collect the good fractions of granules passing through the #14/150 mesh through metal detector loads the granules and get uniform sized granules.

Lubrication:

All ingredients are lubricated by using the double cone blender and blend for 10minute at 6rpm.

6.4 Formulation Development Comparative data of various formulations of Metformin

Trail-1

Table No: 15 Formula of Metformin F1

S.NO	INGREDIENTS	QUANTITY (mg)
1	Metformin	500
2	Starch	80
3	Sodium Starch Glycolate	-
4	Talc	66.18
5	Methyl Paraben	1.16
6	Propyl Paraben	0.66
7	Gelatin	2
8	SFP	QS
9	Total	650

Trai-2

Table no:16 Formula of Metformin F2

S.NO	**INGREDIENTS**	**QUANTITY** (mg)
1	Metformin	500
2	Starch	85
3	Sodium Starch Glycolate	-
4	Talc	61.18
5	Methyl Paraben	1.16
6	Propyl Praben	0.66
7	Gelatin	2
8	SFP	QS
9	Total	650

Trail -3

Table No: 17 Formula of Metformin F3

S.NO	**INGREDIENTS**	**QUANTITY** (mg)
1	Metformin	500
2	Starch	90
3	Sodium Starch Glycolate	-
4	Talc	56.18
5	Methyl Paraben	1.16
6	Propyl Praben	0.66
7	Gelatin	2
8	SFP	QS
9	Total	650

Trail-4

Table No: 18 Formula of Metformin F4

S.NO	**INGREDIENTS**	**QUANTITY** (mg)
1	Metformin	500
2	Starch	-
3	Sodium Starch Glycolate	6.20
4	Talc	139.98
5	Methyl Paraben	1.16
6	Propyl Paraben	0.66
7	Gelatin	2
8	SFP	QS
9	Total	650

Trail- 5

Table No: 19 Formula of Metformin F5

S.NO	**INGREDIENTS**	**QUANTITY** (mg)
1	Metformin	500
2	starch	-
3	Sodiun Starch Glycolate	6.25
4	Talc	139.93
5	Methyl Paraben	1.16
6	Propyl Paraben	0.66
7	Gelatin	2
8	SFP	QS
9	Total	650

Trail No: 6

Table No: 20 Formula of Metformin F6

S.NO	**INGREDIENTS**	**QUANTITY** (mg)
1	Metformin	500
2	Starch	-
3	Sodium Starch Glycolate	6.20
4	Talc	139.88
5	Methyl Paraben	1.16
6	Propyl Paraben	0.66
7	Gelatin	2
8	SFP	QS
9	Total	650

Trail – 7

Table No: 21 Formula of Metformin F7

S.NO	**INGREDIENTS**	**QUANTITY** (mg)
1	Metformin	500
2	Starch	80
3	Sodium Starch Glycolate	6.25
4	Talc	59.98
5	Methyl Paraben	1.16
6	Propyl Paraben	0.66
7	Gelatin	2
8	SFP	QS
9	Total	650

Trail No – 8

Table No: 22 Formula of Metformin F8

S.NO	**INGREDIENTS**	**QUANTITY** (mg)
1	Metformin	500
2	Starch	85
3	Sodium Starch Glycolate	6.20
4	Talc	54.93
5	Methyl Paraben	1.16
6	Propyl Paraben	0.66
7	Gelatin	2
8	SFP	QS
9	Total	650

Trail – 9

Table No: 23 Formulation of Metformin F9

S.NO	**INGREDIENTS**	**QUANTITY** (mg)
1	Metformin	500
2	Starch	90
3	Sodium Starch Glycolate	6.25
4	Talc	50.18
5	Methyl Paraben	1.16
6	Propyl Paraben	0.66
7	Gelatin	2
8	SFP	QS
9	Total	650

COMPARATIVE DATA OF NINE FORMULATIONS OF METFORMIN (n=9)

Table no: 24 Comparative data of nine formulations of Metformin

INGREDIENTS	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Metformin	500	500	500	500	500	500	500	500	500
Starch	80	85	90	-	-	-	80	85	90
Sodium starch glycolate	-	-	-	6.20	6.25	6.20	6.25	6.20	6.25
Talc	66.18	61.18	56.18	139.98	130.93	139.88	59.98	54.93	50.18
Methyl paraben	1.16	1.16	1.16	1.16	1.16	1.16	1.16	1.16	1.16
Propyl paraben	0.66	0.66	0.66	0.66	0.66	0.66	0.66	0.66	0.66
Gelatin	2	2	2	2	2	2	2	2	2
SFP	QS	QS	QS	QS	QS	QS	QS	QS	QS
Total	650	650	650	650	650	650	650	650	650

6.5 COMPRESION OF TABLETS

Compression parameters:-

The compression is done by using CADMACH 45 station compression machine specially designed for the compression of tablets having two different hoppers for the flow of granules. Two punches are setting in the compression machine for the compression of the tablets. The pressure adjustment devises are used to adjust the pressure in the machine. It helps to adjust the weight of the tablet. The granules are passed through the two hoppers, and are filled in the die cavity and the final compression takes place with desired weight and the hardness being set. Due to the pressure on the upper and the lower punch the granules are compressed to get the tablet.

Weight and the content uniformity of tablet are tested.

Punch specification:-

Upper punch: 6mm plain round with biweled edeges and kg embossed upper punch

Lower punch: 6mm plain round with biweled edeges lower punch

Temperature and relative humidity record

Temperature: 25-26^{0}C

Relative Humidity: 46-47%

Compression parameter

Description of tablet – White coloured , round, biweled edges and kg embossed.

Weight of tablet - 650±5%

Hardness – 8mm

Friability – NMT 0.8%

Disintegration time – NMT 15min

6.6 POST COMPRESSION PARAMETERS[38,39]

The quantitative evaluation and assessment of a tablets chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. These properties are important since chemical breakdown or interaction between tablet components may alter the physical tablet properties, and greatly effect the bioavailability of the tablet system. There are various standards that have been set in the various pharmacopeias regarding the quality of pharmaceutical tablets. This includes the diameter, size, shape, thickness, weight, hardness, disintegration and dissolution characters. The diameter and the shape depend on the die and punches selected for the compression of tablets. The remaining specifications assure that tablets do not vary from one production lot to another. The following standards or quality control tests should be carried out on compressed tablets.

1. General appearance

The general appearance of tablets, visual identity and overall 'elegance' is essential for consumer acceptance, control of lot-to-lot uniformity and general tablet uniformity and for monitoring the production process. The control of general appearance involves measurement of attributes such as a tablet's size, shape, color, presence or absence of odour, taste, surface textures, physical flaws and consistency.

2. Size and Shape

The type of tooling determines the shape and the dimensions of compressed tablets during the compression process. At a constant compressive load, tablets thickness varies with the changes in die fill, particles size distribution and packing of the powder mix being compressed and with tablet weight, while with a constant die fill, thickness varies with variation in compressive load. Tablet thickness is consistent from batch to batch or within a batch only if the tablet granulation or powder blend is adequately consistent in particle size and particle size distribution, if the punch tooling is of consistent length, and if the tablet press is clean and good working condition.

3. Thickness

The thickness of individual tablet may be measured with a micrometer, which permits accurate measurements and provides information of the variation between the tablets. Tablet thickness should be control within a ±5% variation of a standard value. Any variations within a particular lot of tablets or between manufactures lots should not be apparent to the unaided eye for consumer acceptance of the products. In addition thickness must be controlled to facilitate packaging. The physical dimension of tablet along with the density of the material in the tablet formulation and their propotions, determine the weight of the tablet. The size and the shape of the tablet can also influence the choice of the tablet machine to use, the best particle size for granulation, production l ot size that can be made, the best type of tabletting processing that can be use, packaging operations and the cost of production.

4. Weight variation

This test is also known as uniformity of weight. This does not apply to layer or enteric coated tablet. Weight of individual 20 tablets was noted and their mean weight was calculated, and the percentage deviation was calculated by using the formula.

$$\text{Percentage deviation} = \frac{X - X^1}{X} \times 100$$

Where,

X = actual weight of the tablet

X^1= average weight of the tablet

5. Content uniformity

The content uniformity test is used to ensure that every tablet contain the amount of drug substance intended with little variation among tablet within a batch due to increased awareness of physiological availability. The content uniformity test has been included in the monograph of all coated and uncoated tablets and all capsules intended for oral administration where the ranges of size of the dosage form available include 50mg or smaller sizes. Tablet monograph with a content uniformity requirements do not have weight variation requirements. For content uniformity test respective samples of 30 tablets are selected are 10 are assigned individually at least 9 must assay within 15% of the declared potency and none may exceed ± 25%.

6. Friability

Friction and shock are the forces most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and is designed to evaluate the abilility of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by use of Roche fribilator. A number of tablets are weigh and placed in the apparatus their they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After 4 minute of this treatment of 100 revelations the tablets are weighing and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The values expressed as percentage a maximum weight loss of not more than 1% of the tablet being tested during the friability test is consider generally acceptable and any broken or smashed tablet are not picked up. Normally, when capping occurs friability values are not calculated. A thick tablet may have fewer tendencies to cap whereas thin tablets of large diameter often show expensive capping, thus indicate in that tablets with greater thickness have reduced internal stress.

$$\text{Friability index} = \frac{\text{initial weight} - \text{final weight}}{\text{Initial weight}}$$

7. Hardness

The resistance of tablet to capping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness it now designated as either the Monsanto or stokes hardness tester .The instrument measure the force required to break the tablets when the force generated by a coil spring is applied diametrically to the tablet.

Hardness which is now more appropriately called crushing strength determinations are made during tablet production and are used to determine the need for pressure adjustment on tablet machine. If the tablet is too hard, it may not disintegrate in the required period of time to meet the dissolution specification; if it is too soft, it may not be able to withstand the handling during subsequent processing. Such as coating or packaging and shipping operation. The force required to break the tablet is measured in kilograms and crushing strength of 4kg usually consider to the minimum for satisfactory tablets. Oral tablet normally have the hardness 4- 10kg;However,hypodermic and chewable tablet are usually much softer(3 kg) and some sustained release tablet are much harder(10-20kg).Tablet hardness associated with other tablet properties such as densities and porosity. Hardness generally increases with normal storage of tablet and depends on the shape, chemical properties, binding agents and pressure applied during compression.

8. Dissolution.[40]

Dissolution is the process by which a solid solute enters a solution. In the pharmaceutical industry it may be define as the amount of drug substance that goes in to solution per unit time under standardized conditions of liquid/solid interphase, temperature and solvent composition.

Dissolution behavior drug has a significant effect on pharmacological activity in fact a direct relationship between in vitro dissolution rate of many drugs and their solid dosage forms may or may not disintegrate when they interact with gastro intestinal fluid following oral administration depending on their design.

Dissolution kinetics is important in determining the bioavailability of a drug .A variety of designs of apparatus for dissolution testing have been proposed and tested, varying of simple beaker with stirrer to, complex system with lipid phases and lipid barrier where an attempt is made to mimic the biological milieu. The choice of apparatus to be used depends largely on the physiochemical properties of the dosage forms.

The two types of methods are employed for performing the in vitro dissolution studies

1. Basket type

2. Paddle type

Basket type

Basket method is used to evaluating the formulations that tend to float by carrying out the dissolution study. Plotting can be due to swelling of the formulation by taking some amount of dissolution medium. So, in this method the formulation is entrapped inside the basket that will not allow the formulation to float even if it swells and becomes lighter than the dissolution medium.

Paddle type

Paddle method can be used for floating formulations and those formulations that don't float even after swelling. The dissolution apparatus consists of a cylindrical vessel made of glass or inert transparent material. The volume of the vessel generally used was 900ml.In the vessel dissolution media was taken and the formulation to be evaluated had to be placed in it. A shaft is present which is connected at one end to a motor and the other end to a basket or paddle according to the method employed.

For basket method unless otherwise specified 40 mesh size for the basket was used. The rpm of the shaft was 100 rpm for basket method and 50 rpm for paddle method .In regular intervals of time samples were withdrawn from the vessel and analyzed for the drug release up to each interval by UV visible spectrophotometer. After withdrawing the sample it was replaced with same amount of dissolution medium to maintain sink conditions.

Dissolution of Metformin

Medium : 900ml of phosphate buffer pH 6.8

RPM : 100

Time : 0,5,10,15,30,45

Apparatus : Paddle

Temperature : 37±0.5^{0}C

Preparation of buffer pH 6.8

Solution A: M potassium dihydrogen phosphate

6.8gm of potassium dihydrogen phosphate in 1000ml volumetric flask and dissolve in1000ml of purified water make up to volume with purified water.

Solution B: 1M sodium hydroxide solution

Weigh about 42gm sodium hydroxide pellets in 1000 ml volumetric flask and dissolve .Make up to volume with purified water

Procedure

Medium. 900ml of a0.68 percent w/v solution of potassium dihydrogen phosphate, adjusted to pH 6.8 by the addition of 1M sodium hydroxide, speed: 100 rpm

Withdraw a suitable volume of the medium and filter , dilute suitably with water and measure the absorbance of the resulting solution at the maximum at about 233nm .Calculate the content of Metformin hydrochloride, in the medium taking. 806 as the specific absorbance at 233nm.

Drug content[40]

The drug content of the metformin was found by the method of assay method. The drug content of the Metformin not less than 70% of the stated amount of Metformin hydrochloride.

Procedure

Weigh and powder 20 tablets of Metformin. Weigh a quantity of the powder containing about 0.1 g of Metformin Hydrochloride, shake with 70ml of water for 15minutes, dilute to 100.0ml with water and filter .Dilute 10.0ml of the filtrate to 100.0ml with water.Further dilute 10.0ml to 100.0ml with water and measure the absorbance of the resulting solution at the maximum at about 232nm.Calculate the content of Metformin Hydrochloride taking 798 as the specific absorbance at 232nm.

Calculation

Percentage content of the sample

$$= \frac{\text{Absorbance} \times 10 \times 100 \times 100 \times 100 \times \text{Average weight of the tablet}}{\text{Specific absorbance} \times \text{Weight of one equivalent of tablet} \times 10 \times 10}$$

Drug excipient compatibility study

Before making of formulation the drug and the excipients compatibility is very important. It is necessary to confirm that the drug does not react with the polymers and excipients under the experimental conditions and affect the product shelf life.

Procedure

Drug and excipients are mixed with the different ratio. These mixtures were kept in 5ml white coloured vials. These vials are exposed to the room temperature and 40^0C/75%RH. 2-3gm of blend prepared which filled in 3 vials. Observations were made at zero weeks, 1 month, the samples were withdrawn for analysis of appearance, moisture content, assay and related substance.

7. RESULTS AND DISCUSSION

7.1 PHYSIOCHEMICAL PARAMETERS

1. DESCRIPTION

Table no: 25 Description

RAW MATERIAL	COLOUR	ODOUR	TASTE
Metformin	White	Odorless	Tasteless

2. SOLUBILITY

Table no: 26 Solubility

RAW MATERIAL	SOLUBILITY
Metformin	It is freely soluble in water and 95% alcohol and is practically insoluble in acetone, ether and chloroform. It also freely soluble as HCl salt.

3. pH

Table no: 27 pH

RAW MATERIAL	SOLUTION CONCENTRATION	pH
Metformin	1% aqueous solution of HCl	6.68

4. MELTING POINT

Table no: 28 Melting point

RAW MATERIAL	OBSERVED VALUE
Metformin	222^0 C TO 226^0 C

4. CHEMICAL NATURE

Table no: 29 Chemical nature of Metformin

S.NO	PARAMETERS	METFORMIN
1	Molecular formula	$C_4H_{11}N_5.HCl$
2	Molecular weight	165.63
3	IUPAC name	1,1-Dimethylbiguanide hydrochloride.
4	Chemical nature	Equimolar amounts of dimethylamine and 2-cyanoguanidine are dissolved in toluene with cooling to make a concentrated solution, and an equimolar amount of hydrogen chloride is slowly added. The mixture begins to boil on its own, and after cooling, Metformin hydrochloride precipitates with a 96% yield.

5. HYGROSCOPICITY

Table no: 30 Hygroscopic nature of Metformin

RAW MATERIALS	RESULT
Metformin	Hygroscopic

6. LOSS ON DRYING

Table no: 31 Loss on drying

RAW MATERIAL	OBSERVED LOD
Metformin	Not more than 0.5% determined on 1.0g by drying in an oven at 105^0

7. SIEVE ANALYSIS

Table no: 32 Sieve analysis

RAW MATERIAL	NATURE OF SAMPLE
Metformin	100% pass through the 20#mesh

FLOW PROPERTY MEASUREMENT

8. ANGLE OF REPOSE

Table no: 33 Flow property and corresponding angle of repose

RAW MATERIL (API)	ANGLE OF REPOSE (DEGREES)	FLOW PROPERTIES
Metformin	33.69	Good

9. DENSITY

- **BULK DENSITY**

Table no: 34 Bulk density

RAW MATERIAL (API)	BULK DENSITY(PI) (g/ml)
Metformin	0.714

- **TAPPED DENSITY**

Table no: 34 Tapped density

RAW MATERIAL (API)	TAPPED DENSITY (PI) (g/ml)
Metformin	0.909

- **COMPRESSIBILITY INDEX**

Table no: 36 compressibility index

RAW MATERIAL (API)	COMPRESSIBILITY INDEX (%)	FLOW PROPERTY
Metformin	21.45	Passable

- **HAUSNER RATIO**

Table no: 37 Hausner's ratio

RAW MATERIAL (API)	HAUSNER RATIO	FLOW PROPERTY
Metformin	1.27	Passable

10. DRUG CONTENT

Table no: 38 Drug content

RAW MATERIAL (API)	ASSAY (%)
Metformin	It contains not less than 98.5% and not more than 101.0% of $C_4H_{11}N_5.HCl$

7.2 COMPATIBILITY STUDIES

Table no: 39 Compatibility study of Metformin with excipients

DRUG	EXCIPIENTS	1st DAY	1st WEEK	2nd WEEK	3rd week
		40^0C&75% RH	40^0C&75% RH	40^0C&75% RH	40^0C&75% RH
M	STARCH	ND	ND	ND	ND
M	GELATIN	ND	ND	ND	ND
M	METHYL PARABEN	ND	ND	ND	ND
M	PROPYL PARABEN	ND	ND	ND	ND
M	SFP	ND	ND	ND	ND
M	TALC	ND	ND	ND	ND
M	SODIUM STARCH GLYCLOLATE	ND	ND	ND	ND

Where,

M=Metformin

RH=Relative humidity

ND=Change not detectable

Figure no; 3 FTIR spectra of pure Metformin tablet.

Kerala state drug and pharmaceutical limited

Sample name: Metformin hydrochloride
Division : QC
Creation date:18/3/2016
Data array type: linear
Horizontal : Wave number (cm-1)
Vertical : % Transmittance
Acquired by : Analyst

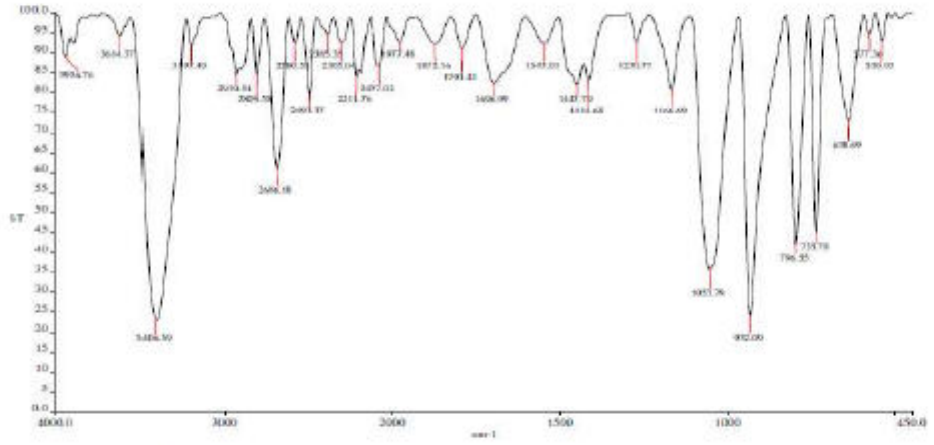
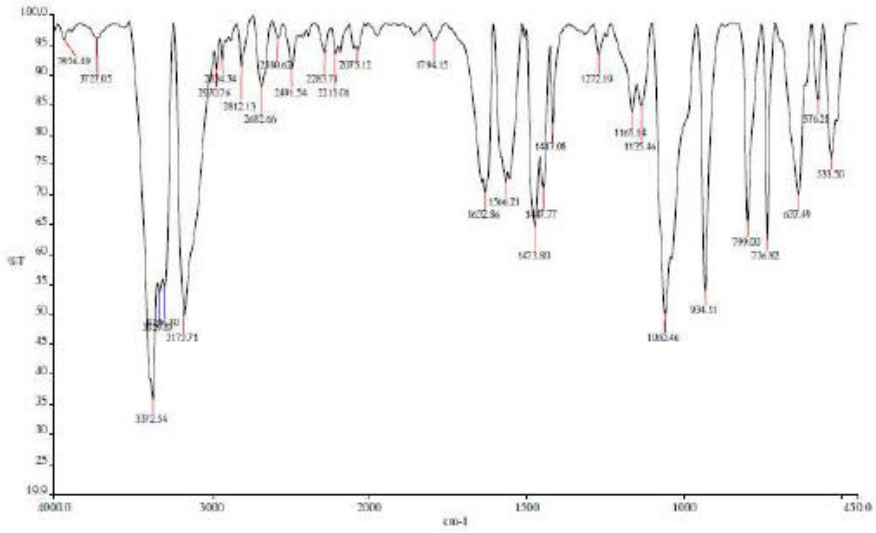


Figure no: 4 FTIR spectrum of optimized formulation.

Kerala state drug and pharmaceutical limited

Sample name : optimized formulation
Division :QC
Creation date:18/3/2016
Data array type: linear type
Horizontal :Wave number(cm-1)
Vertical : % Transmittance
Acquired by : Analyst



7.3 PRECOMPRESSION PARAMETERS OF METFORMIN TABLETS

Table No: 40 Pre compression parameter of Metformin granules trials:

Formulations	Bulk density ($gm/cm^{2)}$	Tapped density (gm/cm^2)	C.I (%)	Angle of repose(^{0})	H.R	Moisture content
F1	0.72	0.90	20.0	$35^0.41'$	1.25	0.0213
F2	0.702	0.93	23.22	$37^0.95'$	1.32	0.0235
F3	0.714	0.95	24.84	$42^0.23'$	1.2	0.026
F4	0.710	0.83	14.45	$45^0.72'$	1.16	0.0231
F5	0.68	0.79	13.92	$38^{0.}95'$	1.16	0.0245
F6	0.57	0.67	14.92	$43^0.55$	1.17	0.022
F7	0.59	0.68	13.23	$31^0.63'$	0.09	0.219
F8	0.710	0.82	13.41	$32^0.23'$	1.15	0.274
F9	0.8	0.912	12.28	$33^0.69$	1.14	0.274

Inference: Formulations F_1 to F_3 has showing the significant flowproperty,angle of repose and hausner's ratio because of the absence of sodium starch glycolate and inclusion of starch.and in case of F4-F6 has indicating the high angle of repose due to the poor flow property in the absence of starch.F7-f9 shown good flow as indicating the less angle of repose because of increase in concencentration of lubricant Sodium starch glycolate and starch also.

7.4 POST COMPRESSION PARAMETER OF METFORMIN TABLETS

Table No: 41 Post compression parameter of Metformin tablets

Formulations	Weight variations (mg)	Hardness (kg/cm^2)	Thickness (mm)	Disintegration Time(min)	Friability (%)
F1	630-684	8	3.64	7	0.05
F2	625-691	7	3.93	9	0.06
F3	609-674	8	4.82	8	0.07
F4	622-688	5	4.56	9	0.08
F5	623-689	9	3.52	8	0.06
F6	610-674	12	3.29	7	0.07
F7	612-676	14	4.86	7	0.05
F8	626-691	9	3.46	8	0.07
F9	621-687	8	4.56	8	0.06
Innovator (Glucophage)	550-600	11	3	9	0.04

7.5 DRUG CONTENT

Table No: 42 Drug Content Values of Metformin

FORMULATION	METFORMIN
F6	88.53
F7	95.43
F8	96.64
F9	96.44

Calculation of drug content value of Metformin

Percentage content of the sample

$$= \frac{\text{Absorbance} \times 10 \times 100 \times 100 \times 100 \times \text{Average weight of the tablet}}{\text{Specific absorbance} \times \text{Weight of one equivalent of tablet} \times 10 \times 10}$$

Example:- weight of 20 Metformin Hydrochloride tablets =12.723g

Average weight = 0.63615g

Weight of one equivalent sample =0.12653g

Specific absorbance =798

Absorbance factor =7654

Percentage content of the sample =

$$= \frac{7654 \times 10 \times 100 \times 100 \times 100 \times 0.6315}{798 \times 0.12653 \times 10 \times 10}$$

= 96.445%

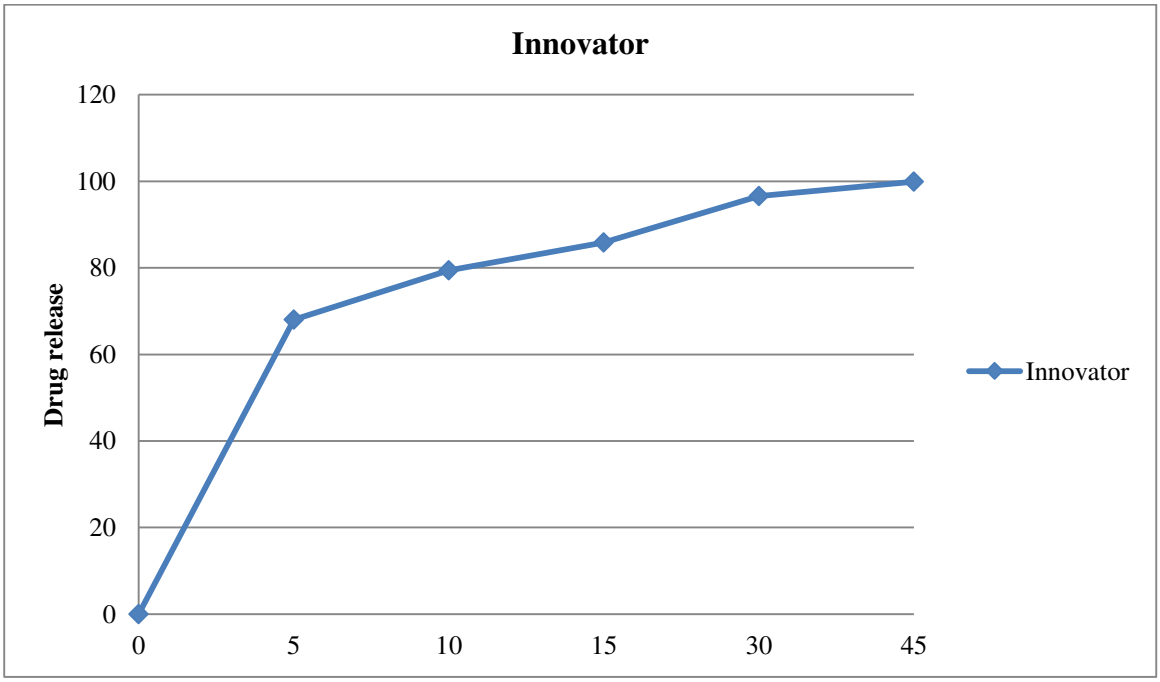
7.6 DRUG RELEASE

7.6.1. INNOVATOR DRUG RELEASE PROFILE

Table No: 43 Innovator drug release profile

Time	Metformin(Innovator)
0	0
5	68.05
10	79.45
15	85.87
30	96.57
45	99.89

Figure no: 5 Release profile of innovator



7.6.2 DRUG RELEASE VALUE OF METFORMIN

Table No: 44 Percentage Drug release value of Metformin

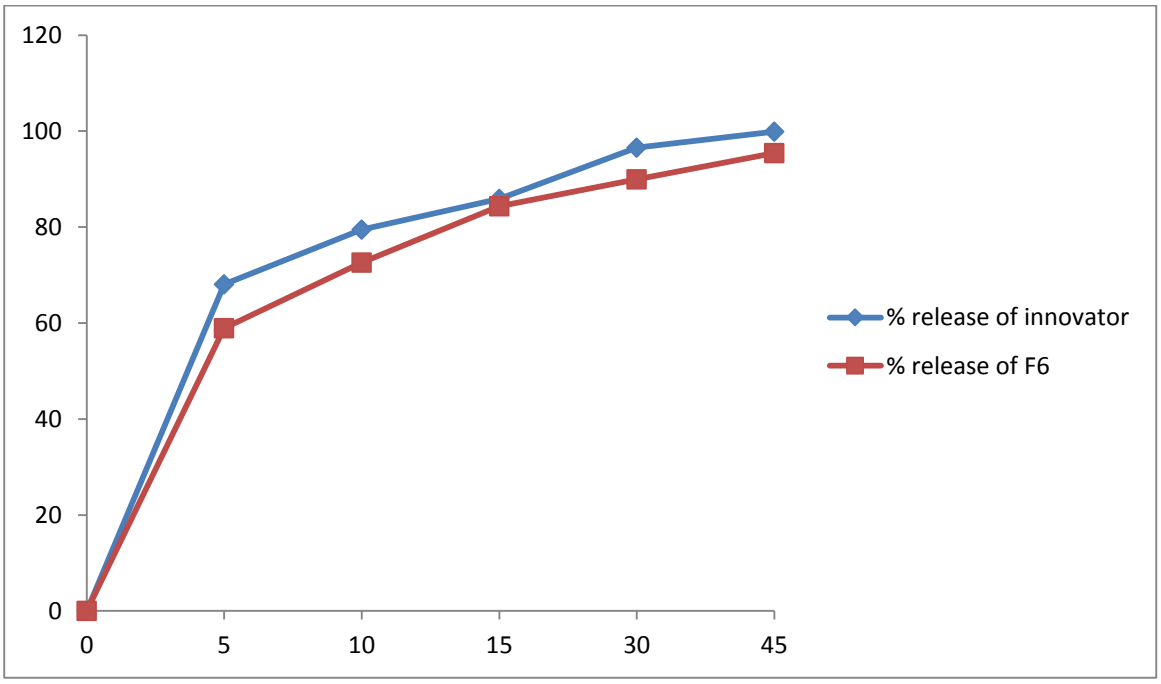
FORMULATIONS	**% drug release of Metformin at 45minutes**
F1	78.42%
F2	84.76%
F3	82.96%
F4	89.43%
F5	83.07%
F6	95.42%
F7	93.09%
F8	96.68%
F9	98.85%

7.6.3 RELEASE PROFILE OF METFORMIN IN F6 COMPARED WITH INNOVATOR

Table No: 45 comparative release of Metformin from innovator and F6

Time	%Release of innovator	% Release from F6
0	0	0
5	68.05	58.93
10	79.45	72.63
15	85.87	84.32
30	96.57	89.95
45	99.89	95.42

Figure No: 6 Release profile of Metformin in F6 compared with innovator



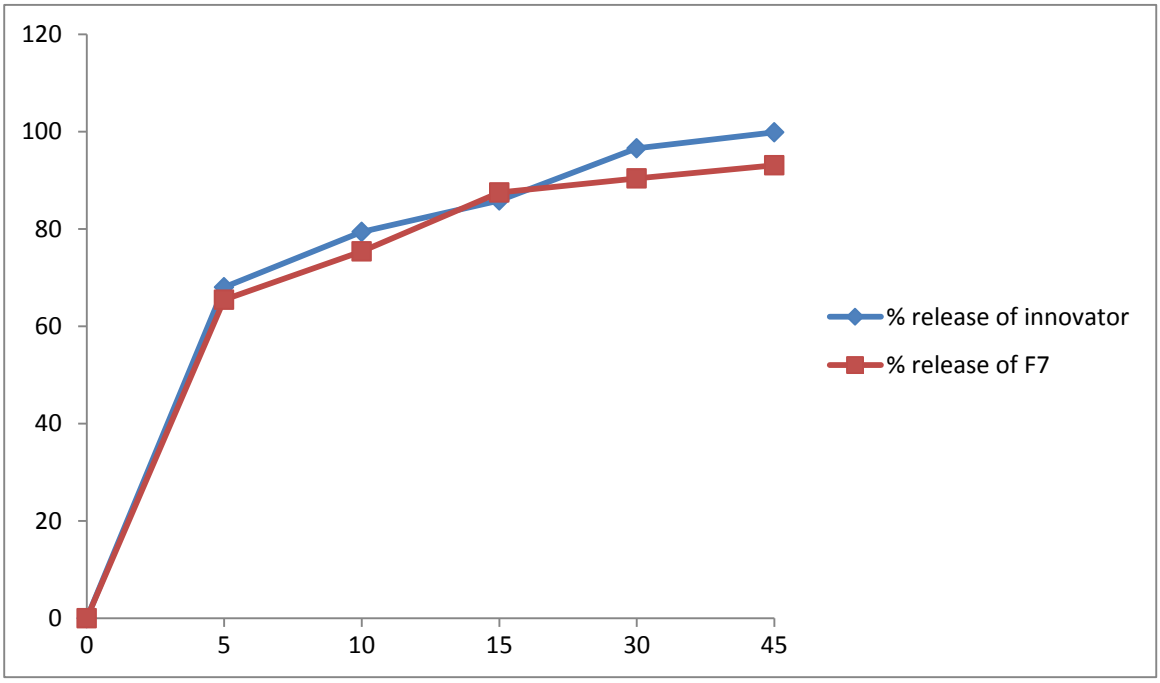
Inference: The release profile of the Metformin from F6 was less than compared to innovator at the end of 45 minutes

7.6.4 RELEASE PROFILE OF METFORMIN IN F7 COMPARED WITH INNOVATOR

Table No: 46 Comparative release of Metformin from innovator and F7

Time(min)	% Release of innovator	% Release from F7
0	0	0
5	68.05	65.45
10	79.45	75.43
15	85.87	87.54
30	96.57	90.42
45	99.89	93.09

Figure No. 7 Release profile of Metformin in F7 compared with innovator



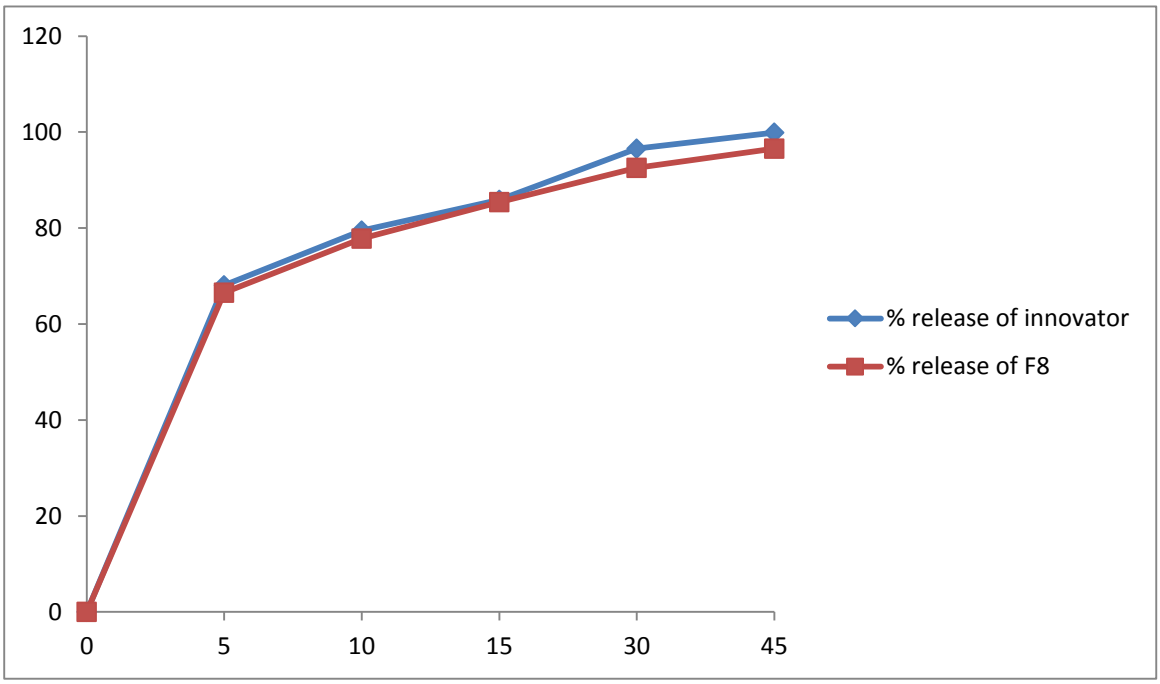
Inference: The release profile of Metformin from F7 was compared to innovator and the release rate was less than the innovator at the end of 45 minutes

7.6.5 RELEASE PROFILE OF METFORMIN IN F8 COMPARED WITH THE INNOVATOR

Table No: 47 Comparitive release of Metformin from innovator and F8

Time(min)	% Release of innovator	%Release from F8
0	0	0
5	68.05	66.53
10	79.45	77.82
15	85.87	85.42
30	96.57	92.53
45	99.89	96.68

Figure No.8 Release profile of Metformin in F8 compared with the innovator



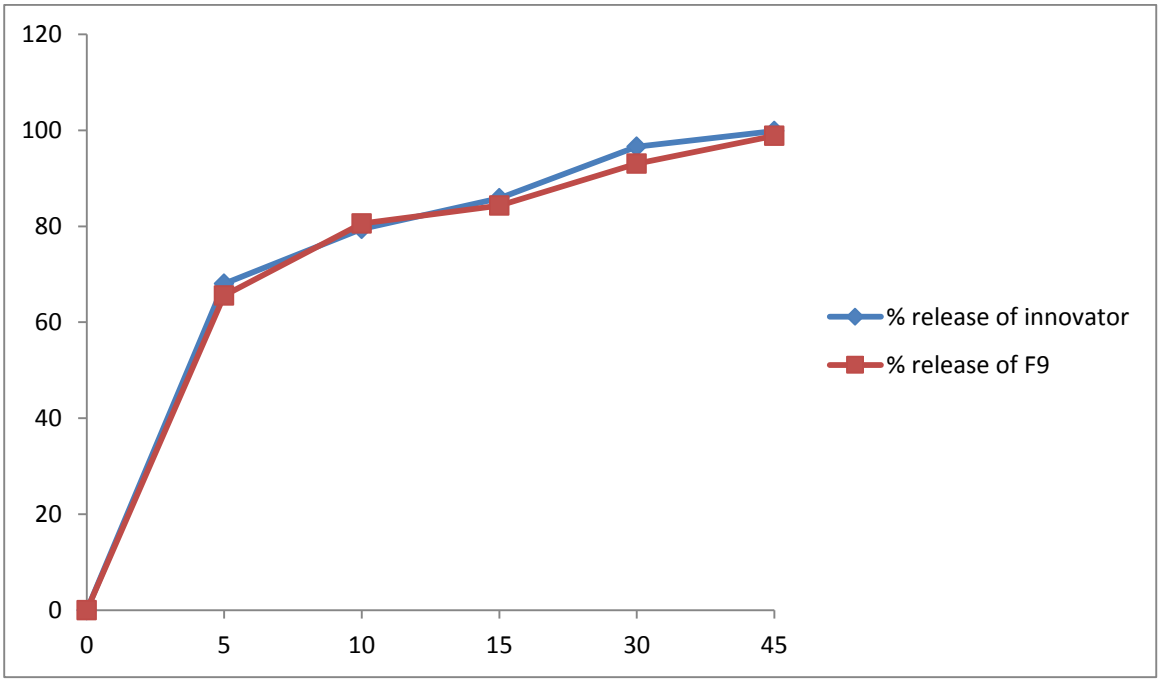
Inference: The release profile of Metformin from F8 was compared with the innovator and the release was compatible to that of innovator at the end of 45 minute.

7.6.6 RELEASE PROFILE OF METFORMIN FROM F9 COMPARED WITH INNOVATOR

Table No: 48 Comparative release of Metformin from innovator and F9

Time(min)	%Release of innovator	% Release from F9
0	0	0
5	68.05	65.54
10	79.45	80.57
15	85.87	84.32
30	96.57	93.05
45	99.89	98.85

Figure No.9 Release profile of Metformin from F9 compared with innovator



Inference: The release profile of Metformin from the F9 was compared with the innovator and the release was almost equal and compatible with innovator at the end of 45 minutes.

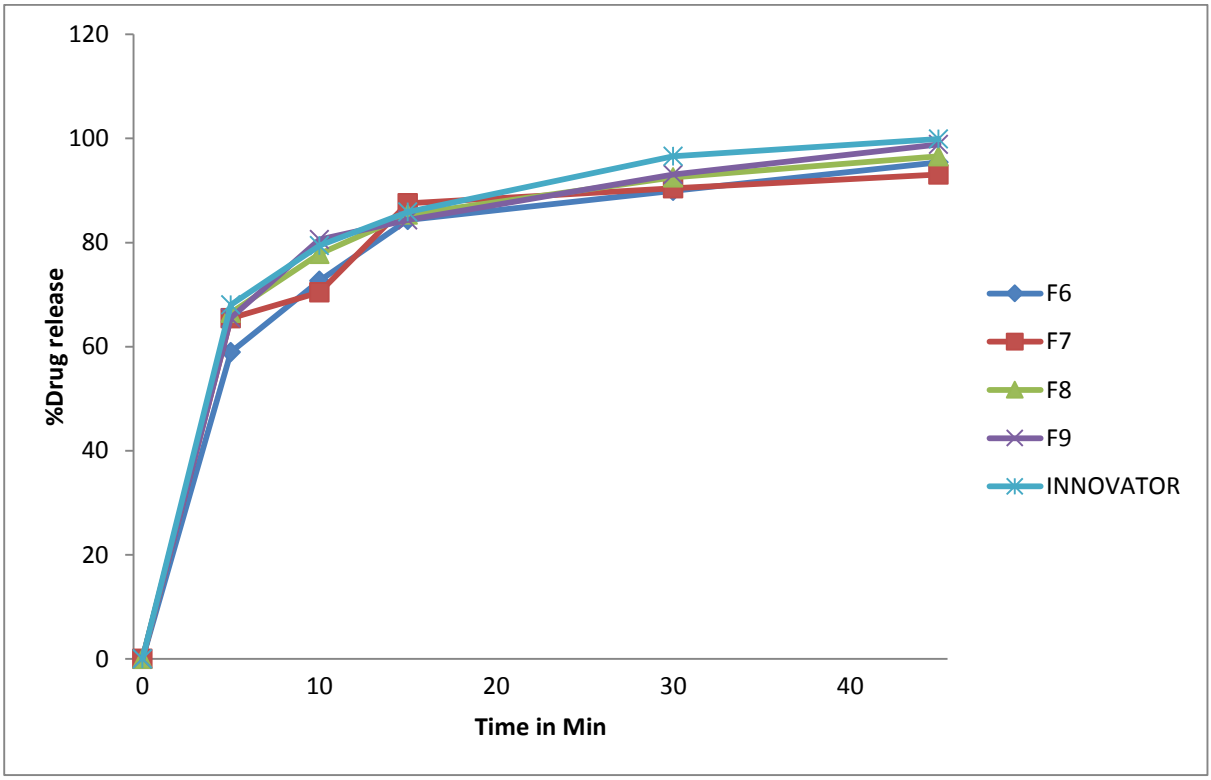
7.6.7 COMPARISON OF DISSOLUTION PROFILE OF FORMULATIONS WITH INNOVATOR

Table No: 49 Comparison of dissolution profile of Metformin formulations with innovator

Time (min)	**Innovator**	**% Drug Release**			
		F_6	**F_7**	**F_8**	**F_9**
5	68.05	58.93	65.45	66.53	65.54
10	79.45	72.63	75.43	77.82	80.57
15	85.87	84.32	87.54	85.42	84.32
30	96.57	89.95	90.42	92.53	93.05
45	99.89	95.42	93.09	96.68	98.85

7.6.8 COMPARITIVE RELEASE PROFILE OF METFORMIN IN VARIOUS FORMULATIONS WITH INNOVATOR

Figure No: 10 Comparitive release profile of Metformin in various formulations with innovator



Inference: Comparitive release profile of Metformin from various formulations showing the release from the F9 matching with the innovator

7.7 STABILITY STUDY

7.7.1 STABILITY DATAS FOR OPTIMIZED FORMULATIONS AT 25^0C&60%RH FOR METFORMIN IMMEDIATE RELEASE TABLET

Table No: 50 Stability data for optimized formulations at 25^0C & 60% RH for Metformin immediate release tablet IP

S.NO	PARAMETERS	STORAGE CONDITIONS (25^0 C& 60% RH)		
		INITIAL	30 DAYS	45 DAYS
1	Description	Weight coloured ,round shaped	N.D	N.D
2	Weight variation	645-655	Within limits	Within limits
3	Hardness	5	5.2	5
4	Thickness	4.9	4.9	4.9
5	Friability	0.32	0.34	0.33
6	Disintegration time	8	8	9
7	Drug release	99.88	99.88	99.87
8	Drug content	650	650	649
9	Moisture content	0.0216	0.0219	0.0321

7.7.2 STABILITY DATA FOR OPTIMIZED FORMULATIONS AT 40^0C &75%RH FOR METFORMIN IMMEDIATE RELEASE TABLET

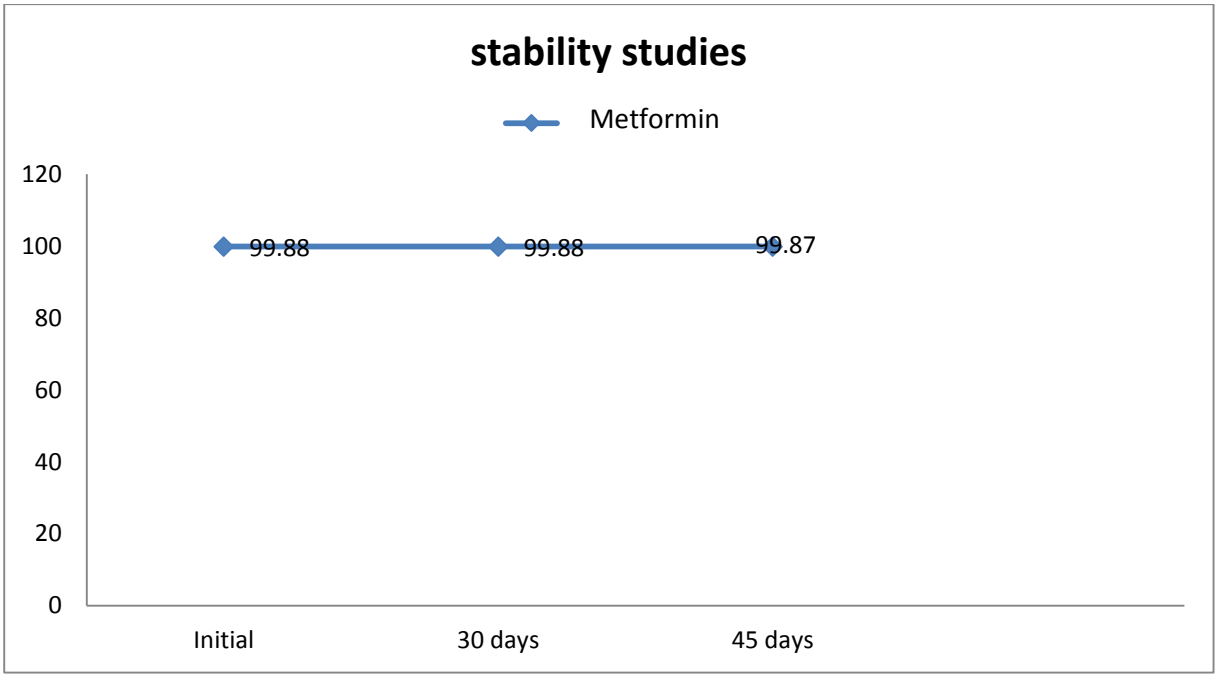
Table No: 51 Stability data for optimized formulations at 40^0C & 75% RH for Metformin immediate release tablet IP

S.NO	PARAMETERS	STORAGE CONDITIONS (40^0 C& 75% RH)		
		INITIAL	30 DAYS	45 DAYS
1	Description	weight colored ,round shaped	N.D	N.D
2	Weight variation	645-655	Within limits	Within limits
3	Hardness	5.3	5.2	5.2
4	Thickness	4.56	4.5	4.5
5	Friability	0.32	0.33	0.33
6	Disintegration time	9	8	8
7	Drug release	99.83	99.83%	99.8%
8	Drug content	650.39	650.05	649.95
9	Moisture content	0.0216	0.0219	0.0231

Table No: 52 Drug release of Metformin at 25^0C & 60% RH

DRUG	% Drug release		
	Initial	30 days	45 days
Metformin	99.88	99.88	99.87

Figure No: 11 Drug release of Metformin at 25^0c&60%RH

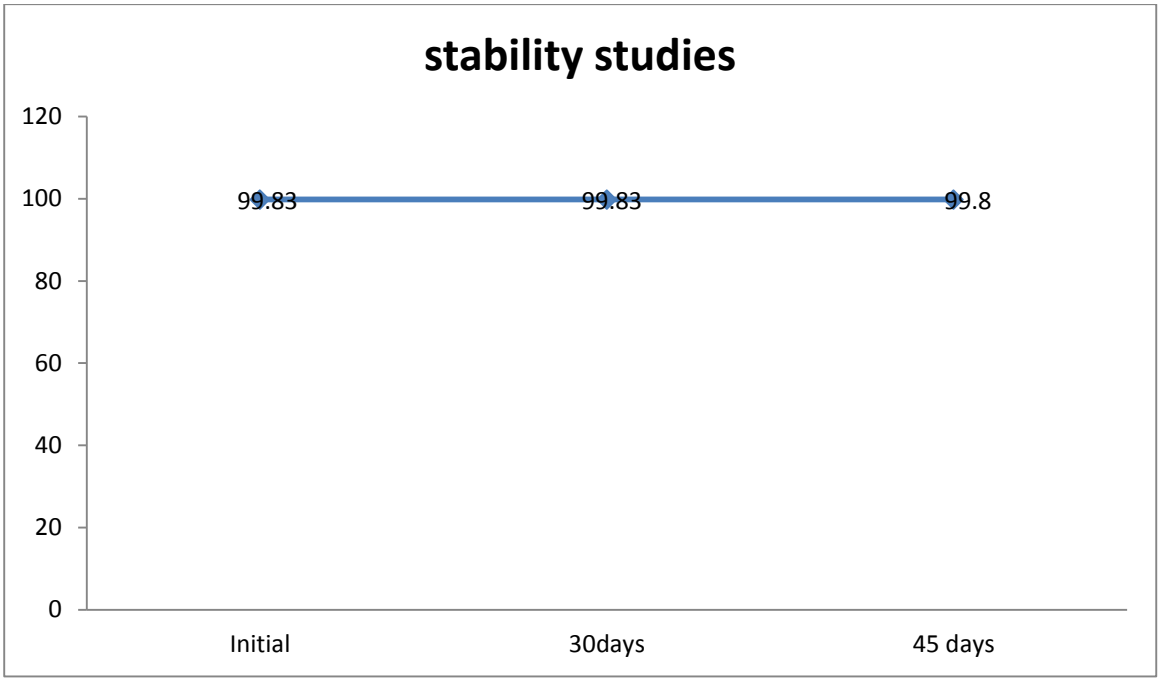


Inference: The drug release was not significantly reduced at the end of 30 days and 45 days storage at 25^0c &60%RH indicating stability of the formulation. All parameters are within the specified limits at the end of the storage.

Table No: 53 Drug release of Metformin at 40^0C & 75% RH

DRUG	% Drug release		
	Initial	30 days	45 days
Metformin	99.83	99.83	99.8

Figure No. 12 Drug release of Metformin at 40^0C & 75% RH



Inference: The drug release was not significantly reduced at the end of 30 days and 45 days storage at 40^0c &75%RH indicating stability of the formulation. All parameters are within the specified limits at the end of the storage.

SUMMARY AND CONCLUSION

The present study was aimed at developing, evaluating and optimization of the oral hypoglycaemic drug Metformin

Totally 9 formulations are prepared by using different ratios of Metformin ,Starch ,Gelatin ,Talc ,Methyl paraben sodium, Propyl paraben sodium and Sodium starch glycolate. Each 9 formulations contain the twenty tablets. The granules are prepared separately in a Max mixer.

Pre compression parameters like Bulk density, True density, Angle of repose indicate all the formulations are showing flow properties. The tablets are compressed by double rotary compression machine and tablets are evaluated for post compression parameters like weight variation, Hardness, Friability, Disintegration and Dissolution parameters.

Formulations F1-F3 sodium starch glycolate is not used, in that formulations starch is used in definite proportions. F4-F6 sodium starch glycolate is used and the starch is not use in this formulations. Sodium starch glycolate and starch used in case of F7-F9. These formulations can be compared to innovator. In the formulation of F9 is more matched to the innovator (Metformin) according to the drug release profile. A good result is getting by using both sodium starch glycolate and starch. The F9 formulation contains Metformin- 500mg, starch-90mg, Sodium Starch Glycolte-6.25mg, Talc-50.18, Methyl Paraben-1.16, Propyl Paraben-0.66mg, Gelatin-2mg.

The compressed tablets are subjected to stability studies at 40^0C and 75%RH, 25^0C and 60%RH. Samples were analyzed at regular intervals as mentioned in stability protocol.

From the study, it may be concluded that formulation F9 (it contains both sodium starch glycolate and starch in suitable proportions) can be prepared as immediate release formulation compared to conventional formulation.

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